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C-Peptide is Relevant in Type 1 Diabetes and its Complications: Summary and Conclusions to the Special Issue

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It has been very satisfying to put together this Special Edition of *The Review of Diabetic Studies* on C-peptide and diabetes. We are greatly encouraged by the advances being made in this research area, and especially to see the beneficial effects of C-peptide making their way into clinic. Once regarded as a redundant waste product of insulin synthesis, C-peptide is now recognized as an important regulatory hormone in its own right. Our understanding of C-peptide physiology is expanding rapidly. It is abundantly clear that C-peptide deficiency in type 1 diabetes plays important pathogenetic roles in the development of various complications, with consequent beneficial effects upon C-peptide replacement.

Over the last decade and a half, a wealth of new information has accumulated regarding C-peptide's interaction with a variety of cell types, its intracellular signaling mechanisms, and its impact on specific cell functions, as well as growth and cell death. It also emerges from these reviews that several questions remain, e.g. the conundrum of C-peptide's interaction with the cell membrane remains unresolved. Is there a C-peptide receptor which, to date, has escaped detection? It is clear that C-peptide binds to cell membranes and accumulates in endosomes in the cytoplasm. Also, it exerts effects on major signaling pathways such as the MAPK and PI-3 kinase pathways with fundamental influences on Na^+/K^+-ATPase and eNOS acivities. These activities affect renal, peripheral nerve, and vascular functions.

Another effect of C-peptide is the regulation of a variety of transcription factors, with impacts on gene and protein expression of structural and functional proteins in the central and peripheral nervous systems, and in renal tissues. Such effects have led to the suggestion that C-peptide may interact with insulin-signaling activities, which in certain cell-systems can be abolished with Wortmannin, but not in others. There is also evidence showing that C-peptide exerts its cellular signaling via a G-protein-coupled receptor, since its signal can be abolished in the presence of pertussis toxin. Interestingly, some of the pepide's activities are operative in the absence of insulin, as in red blood cells and rheological functions. Instead, C-peptide seems to exert such effects by binding to Zn^{2+}-ions, suggesting a charge-specific interaction. Recent observations demonstrate that the peptide is capable of disaggregating insulin hexamers. This effect may be important in relation to exocytosis of insulin from the beta-cells.

One of the transcription factors regulated by C-peptide is NF-κB with downstream effects on inflammatory properties in the vasculature and the central nervous system. Such effects occur in the absence of any effect on hyperglycemia. Perturba-

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tions of several transcription factors influence oxidative stress and apoptotic activities. Hence, C-peptide exerts anti-inflammatory and anti-apoptotic effects in several target tissues of type 1 diabetes complications. The major thrust of the research activities regarding C-peptide physiology has concerned its effects on microvascular complications of type 1 diabetes. In the type 2 diabetic situation, C-peptide effects have not yet been fully explored. Thus, elevated levels of C-peptide may possibly have adverse effects on atherogenesis and on red blood cell ATP synthesis with downstream effects on platelet and endothelial functions. On the other hand, reports also show that C-peptide is capable of preventing intimal hyperplasia and occlusion of vascular grafts.

The beneficial effects of C-peptide on the chronic complications in type 1 diabetic patients have been repeatedly documented with respect to microvascular circulation, as well as renal and peripheral nerve complications. The mechanisms underlying these beneficial effects appear to vary in different tissues, and insulin is not always necessary for C-peptide to function. Furthermore, the physiological effects of C-peptide are conveyed within a narrow concentration range.

Based on present knowledge, we can envisage that replacement of C-peptide, the second missing hormone in type 1 diabetes, may have a major impact in the prevention and treatment of the dreaded complications of diabetes. Proof of concept has been demonstrated. The principle of replacement therapy is not new, but is the basic rationale for the treatment of a number of endocrinological disorders. There are compelling reasons to call for responsible national agencies, patient interest groups, and the pharmaceutical industry to engage, and to promote large scale clinical trials. This would provide an early opportunity for the increasing type 1 diabetes population to benefit soon from therapy with this peptide.

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